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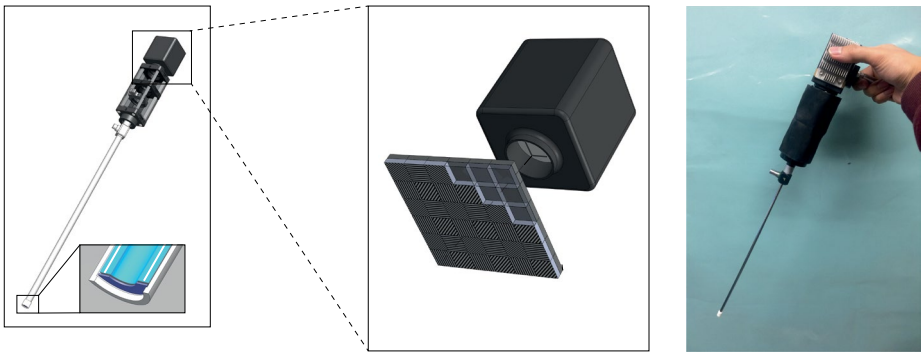
Squeezing more out from clinical imaging

Leveraging or improving established technology for clinical imaging to extract additional physiological information can enhance the quality of the subsequent assessments and widen the technology's uses.



A handheld endoscope for the imaging of cancerous laryngeal lesions via differences in the light-polarization properties of cancerous and healthy tissues. Figure adapted with permission from the Article by Qi, Stoyanov, Elson and colleagues, Springer Nature Ltd.

There are many ways to acquire more biomedically useful information through imaging. Higher imaging resolution, sensitivity and specificity, when feasible, nearly always helps. Increasing the field of view and the number of images taken within the desired volume simultaneously or serially can also be beneficial. Indeed, capturing finer details and subtler changes at the molecular, cellular or tissue levels can provide valuable insights into health status and disease, and into disease progression. Another common strategy to increase the density of informational content in imaging data is the simultaneous imaging of multiple complementary disease biomarkers by using more than one source of contrast. Moreover, multiple signals can be acquired from the same field of view — the common example being the acquisition of complementary anatomical and functional information. Such 'multiplexing' of information can take various forms[1,2]: the acquisition of multiple signals in the same way (for example, the use of two near-infrared probes with different peak-emission wavelengths), the combination of different imaging modalities (such as positron emission tomography (PET), which provides molecular information with high sensitivity, and magnetic resonance imaging (MRI), which can image soft tissue at high contrast), the acquisition of similar signals by using multiple imaging parameters (such as different pulse sequences in MRI) and the combination of functionalities (such as interventional and diagnostic).

Beyond the interpretation of visual information in medical images, the application of radiomics — the extraction and analysis of a large number of quantitative features (such as the intensity, shape and texture of image voxels) from medical images — may reveal disease-associated patterns or biomarkers. Furthermore, machine-learning models are increasingly developed to analyse, combine and augment imaging datasets[3,4] (however, challenges with the robustness and fairness of the data and the algorithms stand between feasibility testing and clinically robust deployments[5,6]). In this issue of *Nature Biomedical Engineering*, five research Articles illustrate how established clinical-imaging technology can be leveraged to acquire additional information to facilitate the detection or monitoring of cancers and the effects of cancer treatments, the observation of ophthalmic conditions and the study of neurological disorders.

In one Article, Ji Qi, Danail Stoyanov, Daniel Elson and colleagues report improvements in endoscopic imaging to address the unsatisfactory rates of false-negative results in the current standard-of-care for identifying laryngeal lesions, which involves distinguishing suspicious tissue by using contrasts in colour and texture via white-light endoscopy. By capitalizing on differences in the light-polarization properties (retardance and depolarization) of cancerous and healthy tissues, the authors improved a handheld endoscope (by leveraging a tip attachment containing a commercial sensor incorporating an array of linear light polarizers on top of photodiodes; pictured) to generate ten times higher contrast (arising from architectural changes in the tissue) than white-light endoscopy for the real-time discrimination of cancerous lesions in patients diagnosed with squamous cell carcinoma.

Polarized light can also be used to visualize how myopia progresses, by monitoring the pathological remodelling of collagen in the eye's posterior sclera towards an increasingly disordered architecture. However, there is no commercial device for imaging posterior scleral collagen in people (polarization light microscopy can only be used ex vivo). In another Article included in this issue, Leopold Schmetterer and co-authors describe how the sensitivity and accuracy of a functional extension of optical coherence tomography that is sensitive to light polarization, which has been used to image the birefringence of scleral collagen only in small animals, can be improved by reconstructing birefringence images after modulating the polarization states across three successive scans at the same location. With the enhanced technique, the researchers show that scleral birefringence can predict the onset of myopia in guinea pigs and that it is associated with the status of myopia in adult humans.

Image-reconstruction strategies can also extract more information from current clinical systems. A particularly notable example is provided in this issue in an Article by Joaquin Herraiz, Jan Grimm and colleagues. Conventional clinical PET scanners visualize one radiotracer at a time. The researchers show that two PET tracers can be simultaneously visualized with preclinical and clinical systems without any modifications in hardware or image-acquisition software by leveraging the capture of 511 keV annihilation photons (resulting from the radioactive decay of positron-emitting radionuclides) and prompt

γ-ray emission in the same energy window, as they show for the concurrent tracking of two radiolabelled compounds in mice. To achieve this, they developed a method that separates and reconstructs the signals from the detection of two pairs of annihilation photons and of a photon pair and an additional γ-ray photon (the latter are known as 'triple coincidence' events, and are typically considered spurious and not reconstructed). Such multiplexed quantitative imaging of PET radiotracers increases the density of information that can be extracted in each PET scan.

The utility of multiplexed imaging can also be augmented by machine-learning models, as Bernd Pichler and co-authors show for the imaging of the spatial heterogeneity of tumours via multimodal and multiparametric PET–MRI. The authors used machine-learning classifiers trained with data from dynamic PET and multiparametric MRI from mice with subcutaneous colon cancer to predict probability maps of tumour-tissue subtypes (viable, apoptotic, necrotic and fibrotic). Then they applied the trained classifiers to retrospective PET–MRI data of patients with liver metastases from colorectal cancer, finding that the output of the classifiers aligned with the histological characterization of intratumoural tissue subregions.

PET is the gold-standard modality for imaging disease-relevant metabolites; for example, impaired glucose metabolism in the brain has been linked to several neurological disorders. However, it cannot detect metabolite products downstream from the orally administered radiolabelled compound. Hyperpolarized carbon-13 magnetic resonance spectroscopic imaging (MRSI) and deuterium MRSI can be used to quantify the concentration of administered deuterated metabolites and their downstream products, but not of endogenous neurotransmitters (such as glutamate and GABA; the glutamate/GABA–glutamine cyclic metabolic pathway is compromised in many neurological disorders). Petr Bednarik, Wolfgang Bogner and colleagues now show in an Article, also included in this issue, that proton MRSI at 7T, which is compatible with readily available magnetic-resonance hardware, can provide higher sensitivity, chemical specificity, and spatiotemporal resolution than deuterium MRSI for differentiating deuterated glucose and its downstream products and non-deuterated neurotransmitters in the human brain, as they show in healthy volunteers. Quantifying the concentration of both deuterated and non-deuterated metabolites in the brain will aid the study of neurological disorders.

Overall, the highlighted research articles exemplify that improvements in performance can make imaging technology more useful[7] and translationally suitable[8], and that widely available clinical-imaging technology can be harnessed to unlock physiological signals that can enhance the diagnosis and monitoring of disease.

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